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Editorial

Sonographic evaluation of ovarian masses and its therapeutical implications

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The introduction of transvaginal sonography into diagnostic gynecology has dramatically increased the number of surgical procedures for ovarian tumors, especially with the recent expansion of minimal access surgery. Here I will consider some of the factors that have contributed to this development and identify measures to improve the evaluation and treatment of ovarian masses.

Sonographic evaluation of ovarian masses

In diagnostic terms, the ovary represents a particular challenge for the gynecologist because of its considerable histological diversity. This is impressively illustrated by the fact that there are 35 subtypes of ovarian tumors in the histological classification system of genuine neoplasms published by the World Health Organization[1]. In addition, the sonographic appearance of the ovary varies with age and endocrine status (i.e. childhood, premenopause, pregnancy, postmenopause) and even undergoes changes within the menstrual cycle itself[2,3]. This explains why the differential diagnosis of ovarian tumors is so difficult not only for the gynecologist but occasionally also for the pathologist. It has become apparent, from the huge number of functional cysts that have been managed with unnecessarily major surgery[4–6], that improved imaging techniques demand a redefinition of the sonographic features of the normal as well as the pathological ovary. The differentiation between functional tumors and genuine neoplasms is the major stumbling block in the evaluation of cystic ovarian masses[7,8] and implies that pre- and postmenopausal women have to be assessed separately.

Not only does the ovary exhibit a variable morphology throughout the cycle (especially in the premenopause), it also undergoes dramatic changes in blood flow. Indeed, the physiological angiogenesis that occurs around ovulation is often more pronounced than that in neoplastic lesions. This fact alone gives some indication of the diagnostic limitations of Doppler assessment of ovarian tumors, particularly in premenopausal women.

Sonomorphology Bearing in mind the above-mentioned differences in pre- and postmenopausal ovarian tumor morphology, descriptive sonomorphological criteria to differentiate between benign and malignant neoplasms in both groups have been sought. In this regard, a variety of tumor-scoring systems have been developed[9–11]. Although some workers have achieved high predictive values with

such systems for cancers, their clinical value has been questioned[12]. This is mainly due to the varying skill and experience of the investigator, the limited reproducibility of subjective criteria and the frequently time-consuming assessment.

In addition, the usefulness of a tumor score should not be based on its ability to detect advanced ovarian cancers. Identification of stage 1a (FIGO classification) lesions or tumors of low malignant potential is of crucial importance for the early detection and successful treatment of ovarian cancer[13]. Sonomorphological assessment of ovarian masses is also complicated by the fact that the majority of cysts detected in premenopausal women do not exhibit a complex morphology. In fact, 59.8% of all premenopausal ovarian tumors are sonographically simple monolocular cysts[14]. The clinical management of these apparently benign cysts which do not meet any of the criteria of malignancy (ascites or solid parts within cystic areas) is, therefore, highly problematical. Indeed, the simple ovarian cyst represents a diagnostic dilemma because the clinical consequences of a malignancy presenting as a simple cyst have to be considered. There is no doubt that simple

ovarian cysts detected in both pre- and postmenopausal women can turn out to be histologically proven ovarian cancers[2,13–15]. In a recent study, we found that 0.8% of malignancies consisting of 0.3% invasive carcinomas and 0.5% of tumors of low malignant potential presented as simple cysts[14]. When performing a single examination by transvaginal sonography, two-thirds of these ovarian tumors are of a functional nature. The risk for malignancy in a sonographically simple cyst increases with its diameter and the age of the patient[14]. This implies that there is an increased risk of malignancy in simple cysts detected in the postmenopause, although there are no epidemiological data to substantiate this. The other diagnostic extreme in the sonomorphological evaluation of ovarian masses is the tumor with solid parts. On a single transvaginal sonogram, the estimated risk of malignancy or tumors of low malignant potential in cysts with solid parts has to be set at 17% in the premenopausal woman[14]. In the postmenopause, two-thirds of all tumors were found to be malignant[2]. To add further to the confusion, approximately one-third of tumors with this morphology turn out to be functional.

In nearly all premenopausal ovaries, even in those whose function is suppressed by the contraceptive pill, and in up to 14.8% of postmenopausal ovaries[16], small cystic structures within the stroma will be seen on transvaginal sonography. Therefore, the clinician has to take into consideration both the size of the tumor as well as its sonomorphological appearance prior to surgery.

In terms of tumor size, it is necessary to determine a cut-off for intervention to minimize the percentage of surgically removed functional cysts in the premenopause and to reduce the number of unnecessary operations in the postmenopausal patient. The size of follicles varies between 15 and 25 mm. Even using a cut-off value of 30 mm, this arbitrary limit would not exclude functional processes. We found 36.9% of all premenopausal ovarian tumors to be between 30 and 40 mm in diameter and, out of these, 68.2% turned out to be functional[14]. Despite the high number of unruptured follicles and corpus lutea in this subgroup, we would expect it to include about 0.5% ovarian cancers and tumors of low malignant potential. At the other extreme, we found that 27.4% of tumors of ≥ 90 mm in diameter were malignant[14].

One can assume that the larger the tumor the greater the sensitivity and specificity for ovarian cancer, but this does not help us achieve an early detection of ovarian malignancy. We have observed that ovarian tumors of between 30 and 90 mm in diameter represent 93.1% of all ovarian masses[14]. However, 84.9% of all benign neoplastic tumors and 58.7% of all malignancies are found within this size range. From the point of view of clinical intervention, we regard a cut-off value of 30 mm (mean diameter) as a clinical compromise.

An additional sonographic sign indicative of malignancy, such as free fluid in the cul-de-sac, is only appropriate for the diagnosis of advanced ovarian cancers. The frequency of free fluid associated with tumors of low malignant potential was found to be 11.1%. This percentage does not differ significantly from 13% found in women with functional tumors and from 9.4% in benign neoplasms. We found that, out of nine postmenopausal tumors of low malignant potential, none had free fluid in the cul-de-sac, whereas 5.4% of benign neoplasms were associated with this sonographic sign[2]. Comparable results have been found in FIGO stage 1a ovarian cancers.

Summarizing this data, it has to be accepted that even the most sophisticated sonomorphological evaluation does not allow a reliable prediction of the presence of ovarian cancer (Figures 1 and 2)[17]. However, a combination of morphology and cyst size provides a rough potential risk for malignancy in each individual case.

(Color) Doppler sonography The initial results obtained from Doppler assessment of ovarian vessels were very encouraging[18,19]. However, further application of this

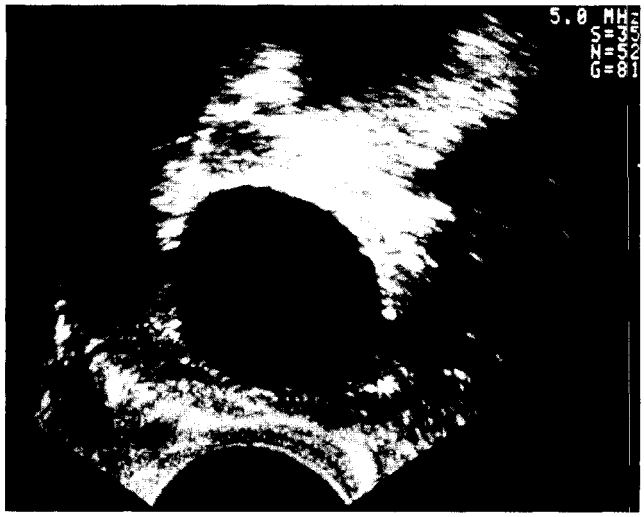

Figure 1 Sonographically simple ovarian cysts; no vessel identified for color Doppler measurement. Histology, ovarian cancer stage Ia

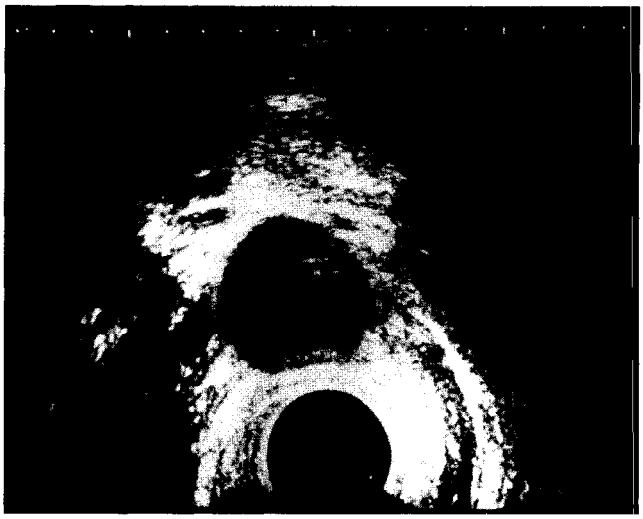

Figure 2 Monolocular cyst with a small papillary vegetation on the inner wall; no vessel identified for color Doppler measurement. Histology, ovarian cancer stage Ia

technique has identified its pitfalls and enthusiasm concerning its usefulness has consequently waned[12,20,21]. One problem is that, in the midcycle, marked perifollicular angiogenesis fulfils all the criteria of tumor angiogenesis. Therefore, as already mentioned, in the premenopause it is difficult to differentiate between functional and neoplastic lesions using Doppler sonography. Furthermore, there is no homogeneous spread of angiogenesis either in the ovarian stroma around the time of ovulation or in the neoplastic lesion. Therefore, the investigator is faced with the problem of selecting the vessel that best represents tumor angiogenesis for Doppler measurements. As a rule of thumb, this vessel can be chosen from one of four main locations:

(1) Peritumorous ovarian stroma (extratumoral);

(2) Tumor surface (potentially extratumoral);

(3) Septa (intratumoral); or

(4) Solid parts within the tumor (intratumoral).

It is evident that the most promising vessel representing tumor angiogenesis has to be within the tumor itself. Extratumoral measurements seem to be of questionable value because the relationship to actual tumor angiogenesis is speculative. However, in about 90% of all malignancies, measurable vessels could be visualized by transvaginal color Doppler imaging[22,23]. The proportion of measurable vessels in benign tumors varies from 54%[22] to 70%[23]. However, in only about two-thirds of ovarian cancers (irrespective of tumor stage) can measurements from intratumoral vessels be achieved[22,24]. In persisting solid-cystic tumors with an intrinsic high rate of malignancy, the clinical relevance of transvaginal color Doppler imaging is academic. On the other hand, in the numerically predominant group of sonographically simple cysts, it would be theoretically desirable to obtain additional information from transvaginal color Doppler imaging, but in 82% of these simple cysts no measurable signals could be found using this technique[25]. Furthermore, it has to be taken into account that all measurements in simple cysts are potentially peritumoral and therefore probably do not reflect angiogenesis. The questionable identity of these so-called 'tumor vessels' offers a good explanation for the great variety of findings and the great overlap of resistance indices (RI) and pulsatility indices (PI) between benign and malignant ovarian tumors.

Comparing follicles, corpus luteum cysts and early ovarian cancers, Bourne and co-workers demonstrated that RI and PI values in functional tumors and early cancers are not significantly different[26]. These findings reflect the limited clinical value of Doppler in the premenopause, and the fact that, in the future, any major clinical impact of transvaginal color Doppler imaging is likely to be confined to the postmenopausal woman. An indispensible prerequisite, however, is the establishment of comparable standards of measurement.

Transvaginal color Doppler can, however, provide some useful additional information. For example, if a vascularization is visualized within a papilliferous excrescence of a complex tumor, it nearly always represents a true neoplasm (either benign or malignant).

Management of the sonographically perceived ovarian mass

Repeat scan For the majority of ovarian tumors, one should always repeat the scan after a certain interval unless clinically unwise to do so. For example, tumors of more than 12 cm diameter (which only account for 3.2% of the total number of ovarian masses) are unlikely to benefit from a repeat scan because they constitute only 0.5% of all functional tumors but 30.2% of all premenopausal malignancies[14]. A follow-up scan after a period of 4–6 weeks enables the detection of spontaneous regression in functional cysts and hence reduces the likelihood of unnecessary surgical intervention[2,27,28]. Between 53 and 89% of all cases of functional cysts will have, however, undergone regression at the repeat scan. High-dose contraceptive pills do not appear to cause significant remission rates of functional cysts[29,30]. If we can assume that spontaneous regression will occur in about 90% of all functional tumors, a repeat scan after 6 weeks should ensure that less than 15% of all patients undergoing surgery will, in fact, have functional cysts.

During the postmenopausal period, especially within the first 5 years, the clinician is faced with another problem: a high incidence (up to 14.8%) of cystic ovarian tumors has been reported of which a significant number of functional cysts (15.7%) should be expected[16]. This is probably due to acyclic residual ovarian activity during this period. Consequently, we would recommend that these women also have a repeat scan after 4–6 weeks.

In general, the requirement for operative histological clarification of even simple ovarian cysts after the menopause is recommended. However, with increasing patient age, the morbidity and mortality of surgical intervention also increase. So the clinician has to weigh up the potential benefit of early operative therapy of a malignant tumor against the risk of unnecessary surgical therapy of a benign harmless cyst.

Although simple cysts show an increased risk of malignancy in the postmenopause compared to the premenopause, there is some evidence that this risk is low for tumors of less than 3 cm in diameter[16,31]. With such cysts, we recommend that patients without a family history of ovarian cancer should undergo expectant clinical management. In cases where the tumor enlarges, surgical intervention should be undertaken as long as the age of the patient, extent of underlying disease, surgical risk and potential risk of malignancy have all been considered. For the individual case, expectant management may be justifiable as long as the cyst remains simple. When complex cystic tumors are detected in postmenopausal women, in spite of the risks associated with surgery, operative therapy should generally be carried out.

Puncturing of cysts As an alternative to surgical therapy, puncturing simple retention cysts is relatively easy and associated with few complications and, therefore, of significant therapeutic value[32–36]. Although, in theory, puncturing may offer considerable clinical benefit particularly in the case of functional cysts, because it is impossible to differentiate accurately between functional and non-functional findings preoperatively, there is always a risk that true neoplasms will be punctured. It is not surprising that, in the latter case, we have to expect an unacceptably high rate of recurrence.

However, cytology as well as tumor markers may not always effectively discriminate between benign and malignant neoplasms[37–41]. Even for functional cysts we have to expect false-positive results. If we measure additional parameters such as estradiol or progesterone, the discrimination of functional cysts can be improved[42,43]. The question of why we should puncture a functional cyst for diagnostic reasons, if we can expect a spontaneous regression in about 90% of cases, remains. Furthermore, it has to be proven whether the remaining 10% of functional tumors still have epithelia that have the capacity for normal hormonal secretion necessary to provide useful diagnostic information as to the nature of the cyst. Thus, we follow the advice of Andolf and co-workers that puncturing ovarian tumors as a therapeutic approach is not appropriate for tumors of unclear etiology[36]. In doubtful cases, an expectant approach seems to be a more reasonable policy.

Surgical approaches The appropriateness of employing minimally invasive methods such as laparoscopy in pre- and postmenopausal women with ovarian masses is in dispute[44–50]. Indeed, there are real risks associated with operating on early ovarian cancer by endoscopic surgery which might lead to tumor cell dispersion within the abdominal cavity[44,51,52]. Blanc and co-workers report an incidence of 1.47% of ovarian malignancies (tumors of low malignant potential and invasive early cancers) in the course of 5307 laparoscopic operations[47].Given the oncological principle that tumor cell spread is directly linked to a deterioration in prognosis[44,53–57], it is up to the operator to decide which surgical approach will incur fewest risks for the patient.

The risk of potential tumor spread varies between 25 and 100% depending on the particular endoscopic approach used. Appropriate use of endobags during ovariectomy reduces the risks associated with intraoperative accidental rupture of the ovarian tumors[58]. However, it should be made sure that tumors in the endobag are only punctured extra-abdominally. These concerns about all minimally invasive approaches in ovarian surgery are supported by findings that CO_2-pneumoperitoneum favors the implantation of tumor cells[59]. Both classical surgery and minimally invasive surgery should fulfil the same prerequisites and therefore meet the following quality control criteria:

(1) An ultrasound examination should be performed by a highly qualified operator before any operation.

(2) Both techniques should be performed by well-trained operators.

(3) The aim of every surgical approach should be the total removal of the ovarian tumor without rupture.

(4) A section of the tumor should be obtained for rapid histological analysis during the course of surgery.

(5) In cases of malignancy, the complete operation should be performed during the same session or within 1 week.

(6) The incidence of unnecessary surgical intervention in cases of functional cysts should not exceed 15%.

(7) The patient should be informed about the special risks associated with the operative approach and about the possibility and significance of tumor cell spread.

The final issue to be addressed is whether the removal of a score of benign tumors is justified by the removal of one ovarian cancer in the premenopause. Although the ratio of 3 : 1 is more favorable in the postmenopause, it must be acknowledged that the intra- and postoperative morbidity is higher in this group. An unanswered question is whether every genuine neoplasm of the ovary must be regarded as being precancerous. This was a clinical dogma for decades but only few data support this hypothesis. It has recently been reported, however, that, especially in cases of serous ovarian cancer, normal epithelia can be found in 22% and borderline lesions in 8%[60]. Therefore, in this most common histological type of ovarian carcinoma (about 60% of all cancers), primary development from the surface epithelium might be assumed to be the most frequent type of pathogenesis[63]. No definitive answer can be given about the importance of benign ovarian tumors in terms of their potential for malignant changes, although one can assume that some ovarian cancers may have had benign precursors even in cases of serous carcinoma. This might justify the histological clarification of an ovarian tumor by surgery even in asymptomatic women.

In conclusion, despite its limitations, sonomorphological and color Doppler evaluation of ovarian masses has a role in reducing the number of unnecessary surgical interventions for simple and functional ovarian tumors and also has the potential for enabling the earlier detection of ovarian cancers.

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